Interference Control in Working Memory Is Associated with Ventrolateral Prefrontal Cortex Volume

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Abstract

■ Goal-irrelevant information may interfere with ongoing task activities if not controlled properly. Evidence suggests that the ability to control interference is connected mainly to the prefrontal cortex (pFC). However, it remains unclear whether gray matter (GM) volume in prefrontal regions influences individual differences in interference control (IC) and if these relationships are affected by aging. Using cross-sectional and longitudinal estimates over a 4- to 5-year period, we examined the relationship between relative IC scores, obtained from a 2-back working memory task, GM volumes, and performance in different cognitive domains. By identifying individuals with either no or high levels of interference, we demonstrated that participants with superior IC had larger volume of the ventrolateral pFC, regardless of participant demographics. The same pattern was observed both at baseline and follow-up. Cross-sectional estimates further showed that interference increased as a function of age, but interference did not change between baseline and follow-up. Similarly, across-sample associations between IC and pFC volume were found in the cross-sectional data, along with no longitudinal change–change relationships. Moreover, relative IC scores could be linked to composite scores of fluid intelligence, indicating that control of interference may relate to performance in expected cognitive domains. These results provide new evidence that a relative IC score can be related to volume of specific and relevant regions within pFC and that this relationship is not modulated by age. This supports a view that the GM volume in these regions plays a role in resisting interference during a working memory task. ■

INTRODUCTION

Working memory (WM) involves control of immediate information and voluntary behavior in a goal-directed manner (Baddeley, 1992). In WM, previously task-relevant, but no longer relevant, information can interfere with new task-relevant information, giving rise to proactive interference (PI; Jonides & Nee, 2006; Hasher & Zacks, 1988). The ability to control goal-irrelevant information, commonly referred to as interference control (IC), is essential for good WM functioning (Bunting, 2006; Lustig, May, & Hasher, 2001; Dempster & Corkill, 1999; May, Hasher, & Kane, 1999). Similar to WM capacity, IC is also linked to fluid intelligence (Burgess, Gray, Conway, & Braver, 2011). In addition, fluid intelligence has been related to differences in 2-back lure trial performance (Shipstead, Harrison, & Engle, 2016), thus affecting the ability to inhibit goal-irrelevant trials. Important to note is that IC is distinct from other types of inhibition, like response inhibition or resistance to distracters (e.g., Friedman & Miyake, 2004).

Executive functions such as IC have been associated with frontal brain regions (Alvarez & Emory, 2006). Larger brain volumes in prefrontal cortex (pFC) have in turn been associated with cognitive functioning (Yuan & Raz, 2014; see also Zimmerman et al., 2006), but whether certain cognitive abilities are specifically linked to one or a limited number of brain regions remains unknown (e.g., Kaup, Mirzakhanian, Jeste, & Eyler, 2011). Instead, executive functions most likely depend on multiple brain regions with separate, but interconnected, components (see Friedman & Miyake, 2017). For instance, network-centric models of brain organization seem to best describe brain activity during response inhibition tasks (Hampshire, 2015; Hampshire & Sharp, 2015). However, there is also evidence that key frontal regions may serve as a flexible hub that coordinates activities within a brain network, based on current task demands (Cole et al., 2013; Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013). Indeed, a coordinating role as shown via formal analysis of causal dynamics has been reported by recent research (Hampshire et al., 2016; Parkin, Hellyer, Leech, & Hampshire, 2015). By this view, individual differences in the ability to control interference may most likely be accounted for by a common brain region that incorporates multiple executive functions. Whether a specific region within pFC can be uniquely involved during control of interference in WM is, however, still under debate (e.g., Aron, Cai, Badre, & Robbins, 2015). Dealing with interference may perhaps not be a result of a domain-specific or domain-general

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involvement, as evidence seems to show that both specific and more general processes work together to resolve cognitive conflict (Hsu, Jaeggi, & Novick, 2017).

Neuroimaging, brain stimulation, and patient studies support a view in which certain frontal regions are linked to IC, such as the ventrolateral pFC (VLPFC; BA 44/BA 45; Nee et al., 2013; Persson, Larsson, & Reuter-Lorenz, 2013; Rottschy et al., 2012; Atkins, Berman, Reuter-Lorenz, Lewis, & Jonides, 2011; Nee & Jonides, 2009; Jonides & Nee, 2006; Badre & Wagner, 2005; Owen, McMillan, Laird, & Bullmore, 2005; D'Esposito, Postle, Jonides, & Smith, 1999). A leading proposal regarding the VLPFC involves postretrieval selection of information, where interference from conflicting information needs to be resolved after recollection (Nee & Jonides, 2009; Badre & Wagner, 2007; Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005). Furthermore, a meta-analysis of neuroimaging functional studies show involvement of both dorsolateral pFC (DLPFC) and VLPFC during IC in WM, but that anterior insula shows the strongest peak activations on average for these kinds of tasks (Rottschy et al., 2012). Indeed, activation in insula has repeatedly been observed in tasks with high demands on IC (Xu, Xu, & Yang, 2016; Cieslik, Mueller, Eickhoff, Langner, & Eickhoff, 2015; Nee, Wager, & Jonides, 2007; Wager et al., 2005; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002), but the role of insula volume in IC is still unknown.

Age-related cognitive deficits include impairments in executive functions (Turner & Spreng, 2012; Buckner, 2004), WM (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012; Bopp & Verhaeghen, 2007; Park et al., 2002; Babcock & Salthouse, 1990), and IC (e.g., Hasher & Zacks, 1988). It has been proposed that age-related impairments in controlling PI may cause poor performance in WM (Nyberg et al., 2012; Bopp & Verhaeghen, 2007; Park et al., 2002; Hasher, Quig, & May, 1997; Babcock & Salthouse, 1990) and other cognitive domains (Yuan, Voelkle, & Raz, 2018; Mishra, Anguera, Ziegler, & Gazzaley, 2013; Kirwan & Stark, 2007). Despite observations of age-related impairments in the ability to control PI in WM (Samrani, Bäckman, & Persson, 2017; Persson et al., 2013; Hasher, Lustig, & Zacks, 2008; McCabe & Hartman, 2008; Stoltzfus, Hasher, & Zacks, 1996), the underlying neural mechanisms for such deficits remain largely unknown. This study was designed to fill this gap in the literature by investigating the association between specific frontal brain volumes and IC using both cross-sectional and longitudinal data from the Betula Study (Nilsson et al., 1997).

IC is often measured as the difference between nonrecent (or nonfamiliar) trials and lure trials within a standard WM task, such as the *n*-back (e.g., Schmiedek, Li, & Lindenberger, 2009), or the item recognition recent probe task (e.g., Oberauer, 2001). In previous work, we have used a relative difference score obtained by calculating the relative difference between nonfamiliar trials and lure trials (Samrani et al., 2017). We believe that such a relative approach reflects a more salient measure of IC effort than calculating a pure RT difference. The main reason being that a relative measure controls for individual differences in basic cognitive skills, such as processing speed (e.g., Salthouse, 1996).

In the current study, we investigate cross-sectional and longitudinal associations between IC and local brain volume in a relatively large sample of individuals across the adult life span. We hypothesize that individuals showing less PI would have larger brain volumes in regions implicated in IC. We also aim to identify a subsample of individuals who are relatively unaffected by PI and examine whether these persons differ from those who respond slower on lure trials compared with nonfamiliar trials. The longitudinal design provides an opportunity to examine change–change relations in brain volumes and IC across a 4- to 5-year time window. In addition, by including data from other cognitive domains (episodic memory, processing speed, fluid intelligence, and verbal fluency), we also investigate IC–cognition associations to evaluate the relevance of our relative interference scores.

METHODS

Participants

Participants were part of a longitudinal population-based study on memory, health, and aging—the Betula Project (Nilsson et al., 1997). Participants were included from samples for which MRI measures were collected in 2008–2010 and 2013–2014. Individuals with clinical dementia and other neurological disorders at baseline were not included. The age of the participants at baseline ranged from 25 to 80 years (mean = 57.8, standard deviation [SD] = 14.1; 48% female), and mean education level was 13.8 years (SD = 4.0 years). Participants were screened with the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), and those scoring 26 and above were included. Two retrospective exclusion criteria were used. First, participants with extremely low performance (proportion hits minus proportion false alarms < .10), indicating a very low adherence to task instructions, were not included. Second, participants with less than three correctly answered lure trials (3-back lures) were not included to obtain a reliable estimate of the outcome measures. Thirty-four participants who did not pass the exclusion criteria for baseline testing but returned for the second time point and passed the performance-based criteria were included at follow-up testing. Thus, the total sample consisted of 200 participants for cross-sectional analyses at baseline, 137 participants for cross-sectional analyses at follow-up, and 103 participants for longitudinal analyses. The Betula Study was approved by the regional ethical review board in Umeå, and written consent was obtained from every participant.

Cognitive Measures

PI was measured using a verbal 2-back WM task, which included familiar lure items (Marklund & Persson, 2012; Gray, Chabris, & Braver, 2003) occurring either one or two trials after the target position (i.e., 3- or 4-back lure; Samrani et al., 2017). The task included 40 trials: 21 non-familiar trials, nine target trials, eight 3-back lures, and two 4-back lures. "Target trials" matched the same stimuli as presented two trials earlier and required a "Yes" response. "Lure trials" consisted of stimuli already presented three or four trials earlier and required a "No" response. "New trials" (Nonfamiliar) were stimuli that had never been presented and required a "No" response. Stimuli and trial conditions were presented in the same fixed order for all participants. Stimuli consisted of Swedish nouns and were presented one at a time for 2.5 sec, with an intertrial interval of 2 sec. For each presented word, participants were instructed to press the "m" key on a standard Swedish keyboard, which corresponds to "Yes" ("Yes, the word I now see has been shown two words ago") and the "x" key for "No" ("No, the word I now see has not been shown two words ago"). Participants were instructed to answer as quickly and accurately as possible.

PI scores were calculated as the relative proportional difference in RT and accuracy between nonfamiliar trials and 3-back familiar trials (lure trials; see Samrani et al., 2017). Interference can thus be observed as the difference in percentage between lure trials (high interference trials) and nonfamiliar trials (no interference trials). For example, an increase in RT or a decrease in accuracy from nonfamiliar to lure trials would reflect being affected by interference, as more time/effort was needed to resolve interference. A relative difference score should represent a more salient measure of executive control, as it takes into account baseline individual differences in the variables in question, such as processing speed (Salthouse, 1996). Interference scores based on RT data are referred to as RT interference scores (RTIS) and interference scores based on accuracy data are referred to as accuracy interference scores (AIS). Median RTs were used to reduce the influence of extreme values.

To examine associations between PI in the *n*-back task and other cognitive functions, several tasks from the Betula Test battery were included. These tasks have been explained in detail elsewhere (Nilsson et al., 1997). A short summary of each task is provided below.

Episodic memory performance was measured by combining five episodic memory tasks. The first two tasks involved immediate free recall of action sentences (16 items each) that were either enacted or rehearsed without enactment. The number of sentences recalled (correct verb and noun) in the enacted and nonenacted conditions were used in the present analysis. In the next two task conditions and following a brief retention interval, participants were asked to recall as many nouns as possible from the sentences described earlier. The four

categories (e.g., fruits, animals) to which each noun belonged served as cues to remember the nouns. The final task was an immediate free recall test of 12 unrelated nouns. The maximum combined score was 76.

The *block design test* was used to estimate fluid IQ. In this test, participants were asked to use colored blocks to produce spatial patterns presented on cards. The raw total number of correct assembled blocks from a total of 51 trials was used (maximum score = 51) in the analyses.

Word fluency was determined by instructing participants to generate as many words as possible, during 60 sec: (1) words starting with the letter "A," (2) five-letter words starting with the letter "M," and (3) names of professions starting with the letter "B."

Processing speed was assessed using three paper-and-pencil tests. In the first task (letter–digit comparison), participants were required to pair letters with digits according to a letter–digit transformation key given on the top of the paper with a time limit of 60 sec. Participants' score was based on the number of correct digits (maximum score = 125). The second task was a speeded comparison task where participants had to decide whether pairs of nonword three- to nine-letter strings were identical or not. Participants' responses were scored for each correctly judged pair during 30 sec (maximum score = 21). The third speed test was similar to the second but involved judging between pairs of abstract line figures during 30 sec (maximum score = 30).

MRI Data Acquisition and Analyses

The MRI data were collected using a 3-T GE scanner, equipped with a 32-channel head coil. The same scanner was used for baseline and follow-up data collection. T1-weighted images were acquired with a 3-D fast spoiled gradient-echo sequence (180 slices with a 1-mm thickness, repetition time = 8.2 msec, echo time = 3.2 msec, flip angle = 12°, field of view = 25 × 25 cm).

To extract gray matter (GM) volumes, T1-weighted images were first processed using FreeSurfer software (Version 5.3.4; surfer.nmr.mgh.harvard.edu). Automated cortical and subcortical parcellation tools in the FreeSurfer software were used for volumetric segmentation, cortical surface reconstruction, and parcellation to quantify the brain volumes of interest. Cortical reconstructions and volumetric segmentations were performed on all images by executing a semiautomatic processing step (recon-all) within this software (Fischl et al., 2002; Dale, Fischl, & Sereno, 1999). Segmentations of subcortical and cortical areas are based on a probabilistic atlas (see below). The processing steps included removal of nonbrain tissue, Talairach transformation, volumetric segmentation, intensity normalization, tessellation of borders between gray and white matter boundaries, applying intensity gradients to localize GM/WM and fluid boundaries in the images. Images from the baseline, together with the follow-up, were processed through the FreeSurfer longitudinal

processing stream, creating a within-subject template for each individual participant, thus increasing the reliability of the segmentation and parcellation of brain regions (Reuter, Schmansky, Rosas, & Fischl, 2012). The cortical ROIs used were based on the Desikan–Killiany atlas in FreeSurfer (Desikan et al., 2006). In addition, GM volume for each ROI was calculated as a sum of corresponding measures in left and right hemispheres.

Selection of ROIs

The GM ROIs were selected based on previously established associations with IC and included the following regions: VLPFC (1) pars triangularis (Nee et al., 2013; Persson et al., 2013; Rottschy et al., 2012; Atkins et al., 2011; Nee & Jonides, 2009; Jonides & Nee, 2006; Badre & Wagner, 2005; Owen et al., 2005; Thompson-Schill et al., 2002; D'Esposito et al., 1999) and (2) pars opercularis (Rottschy et al., 2012; Atkins et al., 2011; Chikazoe et al., 2009; Hamilton & Martin, 2005), DLPFC (3) rostral and (4) caudal middle frontal regions (Dulas & Duarte, 2016; Rottschy et al., 2012; Atkins et al., 2011; Burgess et al., 2011; Nee & Jonides, 2009; Tsuchida & Fellows, 2009), and (5) insula (Xu et al., 2016; Cieslik et al., 2015; Nee et al., 2007, 2013; Rottschy et al., 2012; Dodds, Morein-Zamir, & Robbins, 2011; Wager et al., 2005; Bunge et al., 2002).

Defining Change in Cognition and Brain Volume

The internal consistency and reliability of individual measures included in the composites as well as the interference scores have been taken into account. First, within test reliability for episodic memory, word fluency, block design, and processing speed composite scores are described elsewhere (Cronbach's alpha > .75; Gorbach et al., 2017). Second, test–retest reliability was assessed using Pearson correlation coefficients between time points, for each of the 2-back related scores. The correlations were as follows: RTIS: Pearson's $r = .29$; AIS: Pearson's $r = .45$; target accuracy: Pearson's $r = .44$.

The measure of brain volume change was analyzed as the ratio between baseline and follow-up (i.e., follow-up/baseline). This relative difference score allows for a within-subject standardization of intracranial volume. In addition, the ratio between baseline and follow-up was compared against 0 in a one-way t test to determine general change with age. The change in cognition was also adjusted for baseline differences by using the ratio between baseline and follow-up (i.e., follow-up/baseline).

Statistical Analyses

In addition to correlational analyses between GM volume and interference scores across the whole sample, participants were also divided into a high- and a low-performing group. This classification was determined by using a cutoff based on RTIS performance and consisted of a group of participants that was unaffected by PI (i.e., no significant difference between new and familiar trials) and a group that was affected by PI. Thus, we sampled participants into the high-performance (unaffected) group until RTIS remained below the significance level of $p = .05$. The RTIS cutoff for the group at baseline was 13.5% (unaffected $n = 35$, affected $n = 165$) and 17.5% for the follow-up (unaffected $n = 29$, affected $n = 108$). All participants with an interference score below this level were considered as high performing (i.e., not significantly affected by the interference manipulation; Table 1).

For correlations between general cognition and interference scores, age and education were included as covariates in the models. For all between-group comparisons (MANCOVA), Age and Education were included as covariates. In addition, total intracranial volume (TIV) was included to correct for differences in head size (Jäncke, Mérillat, Liem, & Hänggi, 2015). In the cross-sectional analyses, TIV, Age, and Education were used as covariates. The associations between change in brain volume and change in cognition were analyzed with partial correlations, controlling for age and education. The independent t tests assumed equal variance. Partial eta-squared (η_p^2) was calculated as a measure of effect size. False discovery rate (FDR; Benjamini & Hochberg, 1995) was used to adjust for multiple comparisons. The pericalcarine gyrus of the occipital lobe was used as a control region to determine the specificity of the effects. To evaluate the difference between two dependent correlations, we conducted a one-tailed test of difference, using R software (www.R-project.org/) and the *psych* package (Revelle, 2017).

RESULTS

IC Is Associated with Performance across Cognitive Domains

To test the link between our interference measures and established cognitive tasks, we correlated composite scores from other tasks with our original measures. The AIS was positively correlated with block design and processing speed (Table 2), showing that participants with high ability to control interference also performed well in other cognitive tasks. The association between AIS and episodic memory task was positive, but not significant (Table 2). Target accuracy on the 2-back task was also related to fluency and processing speed, but not to block design or episodic memory (Table 2), indicating a weaker relationship with these cognitive tasks compared with AIS. Lastly, none of the cognitive composite scores were correlated with RTIS after correcting for multiple comparisons (Table 2; all $ps_{(FDR)} > .05$). Similar relationships between AIS and the other measures of cognition were found at follow-up (Table 2) for block design and processing speed, but not for episodic memory or verbal

Table 1. Demographics and Cognitive Scores for the Groups Unaffected and Affected by PI

	Unaffected			Affected			Unaffected Vs. Affected
Variable	M	SD	n	M	SD	n	p
Baseline			35			165	
Sex							ns
Men			23			81	
Women			12			84	
Age	56.0	15.2		58.0	13.8		ns
Education	13.6	4.2		13.8	3.9		ns
TIV (cm^3)	1606.2	164.6		1549.3	149.8		ns
MMSE	28.8	1.1		28.7	1.0		ns
Block design	31.3	9.8		33.1	9.1		ns
Fluency	23.5	7.3		24.6	7.3		ns
Episodic memory	41.5	10.9		43.2	8.1		ns
Processing speed	65.8	17.9		64.9	13.9		ns
Target accuracy	.78	.20		.78	.18		ns
AIS	−.27	.23		−.35	.20		.02
Follow-up			29			108	
Sex							ns
Men			19			54	
Women			10			54	
Age	58.3	14.2		62.2	13.3		ns
Education	15.1	3.7		13.8	3.9		ns
TIV (cm^3)	1606.8	174.2		1567.0	162.1		ns
MMSE	28.7	0.9		28.6	1.0		ns
Block design	33.3	10.7		32.2	8.9		ns
Fluency	25.6	7.9		26.4	8.0		ns
Episodic memory	43.5	8.7		43.4	9.1		ns
Processing speed	56.2	13.8		55.7	11.2		ns
Target accuracy	.82	.20		.83	.17		ns
AIS	−.27	.19		−.35	.19		ns

n = number of participants; ns = nonsignificant (i.e., $p > .05$).

fluency. Target 2-back performance and RTIS did not correlate with any of the cognitive scores at follow-up (Table 2; all $ps_{(FDR)} > .05$). We found no significant correlations between change in any of the IC measures or target accuracy, with changes across domain cognition (all $ps_{(FDR)} > .05$).

We also tested whether AIS was more strongly correlated to fluid intelligence (block design) compared with target 2-back performance. At baseline, AIS showed a significantly stronger relationship with block design than target 2-back performance ($t = −1.79$, $p = .037$). At follow-up, a similar, but nonsignificant, difference was found ($t = −1.29$, $p = .099$).

Age-Related Changes and Differences in Interference Score

A cross-sectional analysis at baseline using linear regression showed that AIS was reduced as a function of age, (Figure 1; $F(1, 198) = 30.19$, $p < .001$, $R^2 = .13$), indicating that older individuals had a reduced ability to control interference. The relationship between RTIS and Age was,

Table 2. Correlation Matrix for 2-Back Conditions and Cognitive Scores for Each Testing Point Separately, Corrected for Age and Education

2-Back Condition	Block Design	Word Fluency	Episodic memory	Processing Speed	Target Trial Acc.	AIS	RTIS
Baseline (n = 200)							
Target trial accuracy	.09	.18*	.13	.23**	–		
AIS	.25**	.19**	.11	.21**	.17*	–	
RTIS	.08	> −.01	.03	.05	−.02	−.26**	–
Follow-up (n = 137)							
Target trial accuracy	.18	.13	.19	.14	–		
AIS	.31**	.11	.04	.24**	.25**	–	
RTIS	−.01	.16	−.01	.06	−.01	−.22**	–

All p values derived from the correlations on the left side of the vertical black line are adjusted for FDR using Benjamini–Hochberg correction. n = number of participants; acc. = accuracy.

*$p < .05$ (two-tailed).

**$p < .01$ (two-tailed).

however, nonsignificant, $F(1, 198) = 1.17$, $p = .28$. At follow-up, a significant relationship was again found between AIS and Age, $F(1, 135) = 18.44$, $p < .001$, $R^2 = .11$, such that older individuals had a reduced ability to control interference. In contrast to the findings from the baseline assessment, RTIS was negatively related to age, with older individuals showing more interference, $F(1, 135) = 7.52$, $p = .007$, $R^2 = .05$. A repeated-measures one-way ANOVA showed no longitudinal effects of Age for either of the interference scores (AIS, $F(1, 126) = 0.04$, $p = .849$, $\eta_p^2 < .01$; RTIS, $F(1, 126) = 0.09$, $p = .76$, $\eta_p^2 < .01$), indicating that interference did not change between baseline and follow-up.

A Large DLPFC Volume Was Associated with Good IC

Using the whole sample at baseline, none of the ROIs showed a significant relationship between brain volume and target accuracy, AIS, and RTIS after multiple comparison correction (Table 3; all $ps_{(FDR)} > .05$). At follow-up, a negative correlation was found between caudal middle frontal volume ($r = −.24$, $p_{(uncorrected)} = .006$, $p_{(FDR)} = .029$) and RTIS (Figure 2). Less PI was related to a larger caudal middle frontal volume at follow-up. Control analyses showed that there were no volumetric correlations with target accuracy, AIS, and RTIS in the pericalcarine gyrus of the occipital lobe at either time point (all $ps > .05$).

Because the interference score is based on the difference between familiar and nonfamiliar trials, a control analysis was performed to investigate if RTIS–caudal middle frontal correlations depended on nonfamiliar trial RT. We found that nonfamiliar RTs did not correlate with any of the five ROIs (all $ps_{(FDR)} > .05$; caudal middle frontal $r = .06$) or the control region (pericalcarine gyrus $r =$

.04, $p > .05$), showing that the previous effect (RTIS–caudal middle frontal volume) were mainly dependent on the relative difference score and that level differences in nonfamiliar trial RT seem not to explain this relationship.

In addition, we performed complementary analyses to examine whether the classification of individuals into groups of participants with low interference (unaffected by interference) and those with high interference (affected by interference) differed on RTs for nonfamiliar trials, RTs for familiar trials, or both. We found that the affected group was both significantly slower on lure (familiar) trials (Table 4) and responded faster on nonfamiliar trials than the unaffected group. Moreover, although RTs for lure and nonfamiliar trials did not differ significantly in the unaffected group (Table 4), in the affected group, there was a significant difference in RTs between lure and nonfamiliar trials. These results indicate that the affected group had indeed more difficulties in handling PI.

Participants with Higher Ability to Control PI Had Larger Brain Volume Compared with Low-Performing Individuals

The high- and low-performing groups (unaffected vs. affected) did not differ in age, sex, education, TIV, or any of the cognitive composites (Table 1; all $ps_{(FDR)} > .05$) at neither baseline nor follow-up. A multiple logistic regression revealed that the combined effect of age, sex, education, TIV, and all cognitive scores was not significant ($p > .05$), with R^2 predictive values of .086 at baseline and .081 for follow-up.

At baseline, a 5 (ROI) × 2 (group: affected vs. unaffected) repeated-measures ANOVA showed a main effect of ROI, $F(4, 192) = 6.65$, $p < .001$, $\eta_p^2 = .12$, but the main effect of
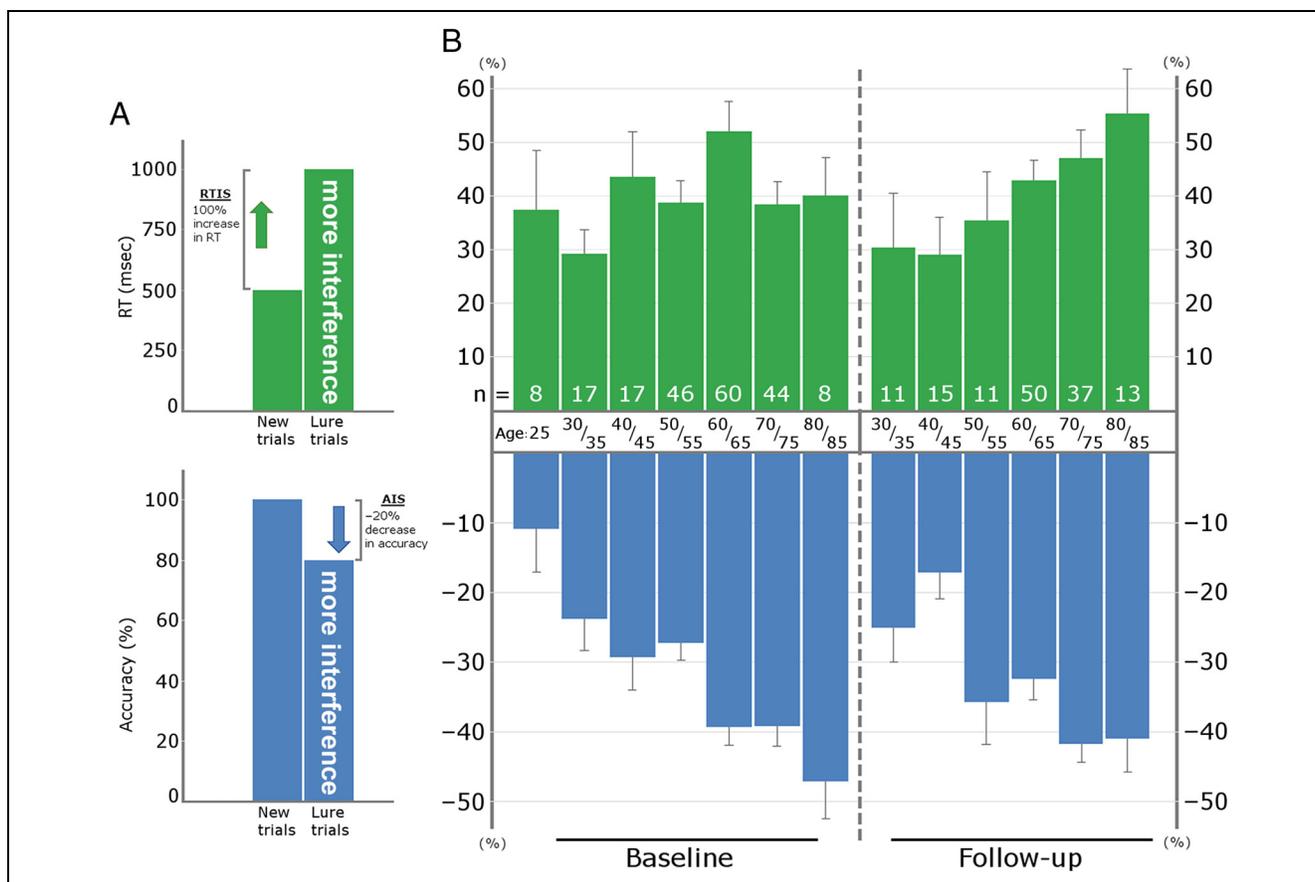
Figure 1. (A) Illustrative description of AIS and RTIS presented on the *y*-axis of B. New trials are nonfamiliar words in a 2-back task, whereas lure trials are words presented at the 3-back position, which is one word later than expected. The relative difference (%-change) between the two trial types, in accuracy and RT separately, accounts for the level of interference. (B) Relative score performance across age for baseline and follow-up, separated with a dotted line. Age groups are made for illustrative purposes, and for each age group, the *n* represents the total amount of participants in that group. The bars represent the standard error of the mean.

Group, $F_{(1, 195)} = 1.53$, $p = .22$, $\eta_p^2 < .01$, and the interaction, $F_{(4, 192)} = 1.82$, $p = .13$, $\eta_p^2 = .04$, were both nonsignificant. At follow-up, the 5 (ROI) × 2 (Group: affected vs. unaffected) repeated-measures ANOVA showed a main effect of ROI, $F_{(4, 129)} = 5.41$, $p < .001$, $\eta_p^2 = .14$, but the main effect of Group, $F_{(1, 132)} = 2.79$, $p = .10$, $\eta_p^2 = .02$, and the interaction, $F_{(4, 129)} = 5.41$, $p = .19$, $\eta_p^2 = .05$, were both nonsignificant. Follow-up analyses using a multivariate ANCOVA showed that, at

baseline, the group with low RTIS (i.e., good IC) had significantly larger pars triangularis volume (Figure 3), $F_{(1, 209)} = 12.83$, $p_{\text{(uncorrected)}} < .001$, $p_{\text{(FDR)}} = .002$, $\eta_p^2 = .06$. At follow-up, unaffected participants had larger volumes of the pars triangularis, $F_{(1, 132)} = 3.91$, $p_{\text{(uncorrected)}} = .050$, $p_{\text{(FDR)}} = .09$, $\eta_p^2 = .03$, and insula, $F_{(1, 132)} = 4.75$, $p_{\text{(uncorrected)}} = .031$, $p_{\text{(FDR)}} = .09$, $\eta_p^2 = .04$. Control analyses showed that there was no volumetric difference between the two groups in the pericalcarine gyrus

Table 3. Correlation Matrix for Brain Regions and 2-Back Performance, Corrected for Age, Education, and TIV

Brain Region	Baseline (n = 200)			Follow-up (n = 137)		
	Target Accuracy	AIS	RTIS	Target Accuracy	AIS	RTIS
Pars opercularis	.03	−.02	−.12	−.02	.06	−.08
Pars triangularis	−.04	−.10	−.08	−.05	−.05	−.02
Caudal middle frontal	.13	.16	.02	.03	−.01	−.24*
Rostral middle frontal	−.09	.08	.09	−.09	−.16	−.02
Insula	>.01	.05	.04	−.06	−.08	−.20

n = number of participants, * = significant *p* values on the 0.5% level (two-tailed) adjusted for FDR using Benjamini–Hochberg correction.
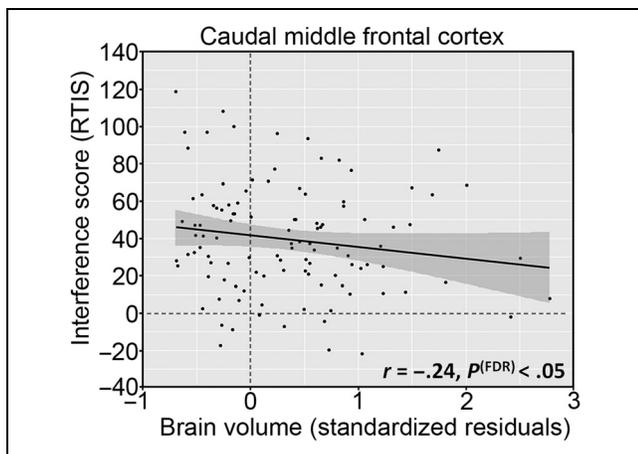
Figure 2. Correlations between RTIS and caudal middle frontal gyrus volume. The RTIS is standardized and corrected for age, education, and TIV.

of the occipital lobe at either time point (baseline: $F(1, 209) = 0.18$, $p = .67$, $\eta_p^2 < .01$; follow-up: $F(1, 132) = 0.14$, $p = .71$, $\eta_p^2 < .01$). The lack of a group by ROI interaction show that the effect in pars triangularis, while showing a significant group difference, is not significantly different from the effect observed in the other frontal regions.

In a follow-up analysis, we separated individuals at baseline depending on regional brain volume to examine whether the group with larger brain volume also had higher IC ability. For this analysis, we focused on the pars triangularis, given that group differences in this region were found in the initial analyzes. The new groups were separated by taking 13.5% of participants with the largest pars triangularis ($n = 27$) and then comparing RTIS score with the 13.5% participants with the smallest pars triangularis ($n = 27$). This analysis showed that the group with larger pars triangularis was less interfered by lure trials than the group with smaller pars triangularis (large volume: mean RTIS = 25.7, $SD = 30.7$; small volume: mean RTIS = 48.1, $SD = 36.1$; $t(52) = 2.47$, $p = .017$), thereby supporting our results where the groups were selected based on behavioral cutoffs.

Change in Brain Volume Was Not Related to Change in IC

In accordance with other studies on aging (e.g., Gorbach et al., 2017) and that age-related changes in cognition are expected only in middle-aged and older adults, analyses of associations between change in IC and brain volume were performed for participants aged 55 years and above ($n = 69$). In line with previous findings (Yuan et al., 2018; Gorbach et al., 2017; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010), average decline in brain volume was significant for all brain regions (all $ps < .05$). However, there were no significant correlations between change in regional brain volume and change in IC (all $ps > .05$). An additional analysis that included participants that declined in IC from baseline to follow-up was performed to examine if a corresponding change in volume could be observed. We found no significant correlation between decreases in RTIS and brain volume change (all $ps > .05$).

Sensitivity Analyses

Individuals who dropped out or did no longer pass the inclusion criteria ($n = 97$) after the baseline assessment were on average older (mean age = 61.4 vs. 54.1, $t(198) = 3.81$, $p < .001$), had lower education (mean education in years = 12.9 vs. 14.6, $t(198) = -3.29$, $p = .001$), had lower MMSE scores (mean score = 28.6 vs. 28.8, $t(198) = -1.98$, $p = .050$), and scored lower on all composite scores than those who remained in the study (block design: mean score= 29.9 vs. 35.5, $t(198) = -4.54$, $p < .001$; episodic memory: mean score = 40.1 vs. 45.6, $t(198) = 4.73$, $p < .001$; processing speed: mean score = 59.9 vs. 70.0, $t(198) = -5.18$, $p < .001$). Dropouts were also less accurate on target trials (mean accuracy = 75% vs. 80%, $t(198) = -2.11$, $p = .036$) and had a lower AIS (mean AIS = -38% vs. -28%, $t(198) = -3.73$, $p < .001$). By contrast, dropouts did not differ from those who remained in the study on RTIS (mean RTIS = 43% vs. 41%, $t(198) = -.35$, $p = .72$) or TIV (mean TIV cm^3 = 1538 vs. 1579, $t(198) = -1.88$, $p = .061$), further indicating the lack of relationship

Table 4. Average Median RT Differences across Nonlure Trial Conditions in a 2-Back Task, Comparing Individuals Affected by Interference against Unaffected Individuals

	Baseline (n = 200)			Follow-up (n = 137)		
	Affected Individuals	Unaffected Individuals	t Value	Affected Individuals	Unaffected Individuals	t Value
Nonfamiliar trial RTs	966 (195)	1208 (316)	5.92**	936 (199)	1150 (289)	4.64**
Lure trial RTs	1433 (304)	1240 (320)	3.36**	1412 (312)	1193 (316)	3.35*
Nonfamiliar vs. Lure	467**	32		476**	43	

All RTs are displayed in milliseconds. Standard deviations are in brackets. n = number of participants.

*$p < .05$.

**$p < .01$.

Figure 3. Between-group differences (unaffected vs. affected) of five a priori-defined brain region volumes. The unaffected group was selected from the total sample on the basis of their very low RTIS in a 2-back task, whereas the remaining individuals having high interference scores were the affected group. The bars represent GM volume standardized residuals, corrected for age, TIV, and education. Each bar includes the standard error of the mean. The *p* values are adjusted for FDR and marked with ** when significant, whereas significant unadjusted values are marked with * (.05 was the threshold of significance).
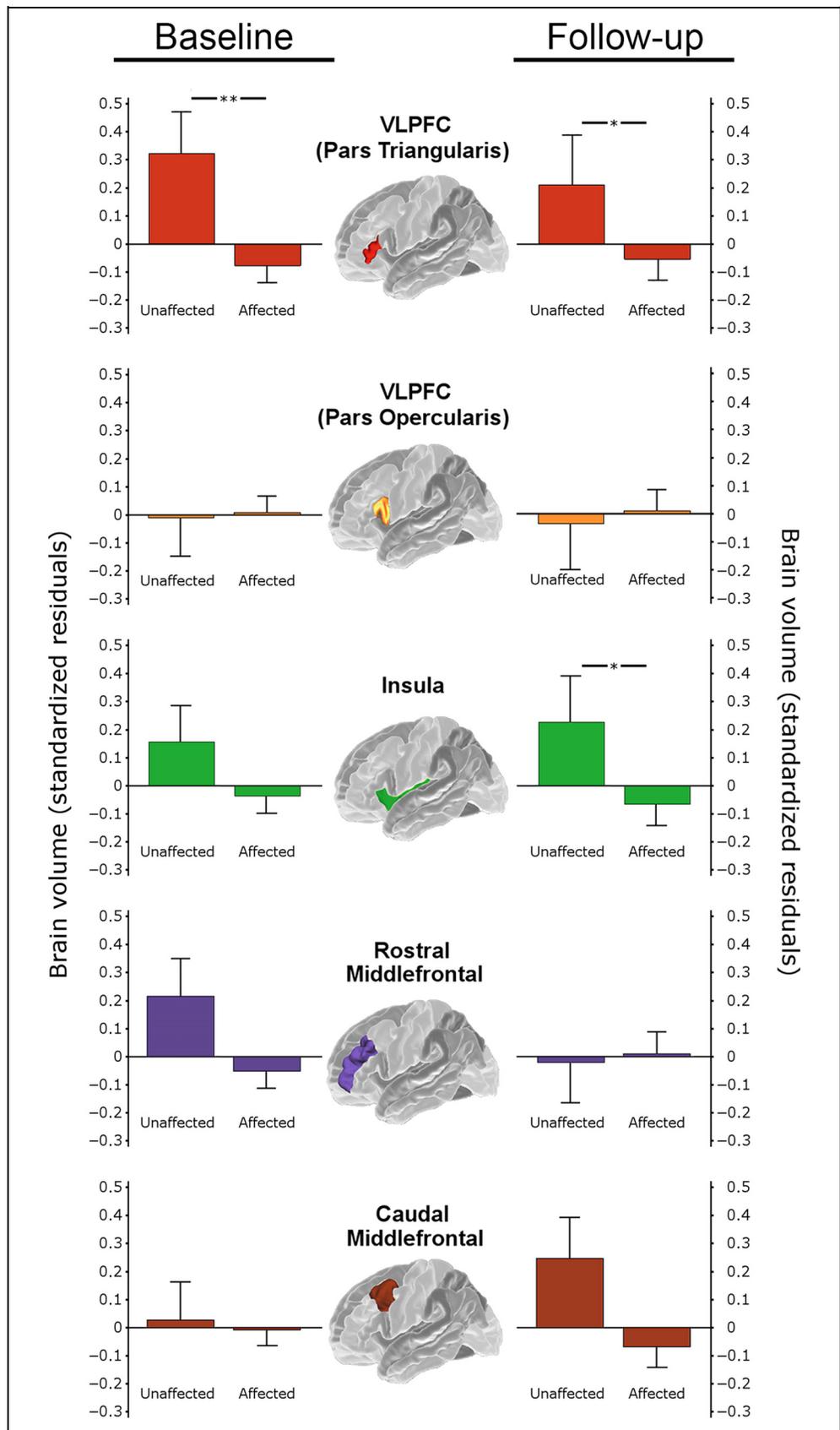
between IC and demographic variables. Note that these analyses were made without including the 34 participants that did not pass the baseline criteria but returned and were included at the follow-up.

DISCUSSION

The primary aim of the current study was to examine whether IC is related to local brain volumes using cross-sectional and longitudinal data. We show that volumes of a subregion in the VLPFC, which has been implicated in IC (Nee et al., 2013; Persson et al., 2013; Rottschy et al., 2012; Atkins et al., 2011; Nee & Jonides, 2009; Jonides & Nee, 2006; Badre & Wagner, 2005; Owen et al., 2005; Thompson-Schill et al., 2002; D'Esposito et al., 1999), was larger in individuals with superior ability to control PI in WM. This relationship was found at both baseline and follow-up. Our research thus extends past work by identifying participants that were relatively unaffected by PI and demonstrating that these individuals had larger volumes in relevant brain regions. None of the findings could be accounted for by differences in age, sex, education, MMSE, cognitive scores, or TIV, indicating that our primary results were relatively specific to our IC measures. Moreover, analyses at follow-up showed that, across the whole sample, local brain volume in DLPFC was positively related to IC. However, longitudinal analyses over 4–5 years did not provide evidence for any relationships between change in local brain volume and change in IC. Also, we replicated earlier results (Samrani et al., 2017; Persson et al., 2013; McCabe & Hartman, 2008; Hasher et al., 2008; Stoltzfus et al., 1996) by showing that older age is related to a lower ability to control interference in WM, although no change in IC was found between baseline and follow-up. Lastly, we provide a link between a specific component of executive control and fluid intelligence, indicating that this estimate may have better measurement properties compared with other commonly used measures of IC.

The current results corroborate previous associations between executive control functions and pFC volume. For example, cross-sectional studies show that composite scores of executive functions and individual measures from the Delis-Kaplan Executive Function System assessment and the WCST are associated with pFC volume (Cardenas et al., 2011; Elderkin-Thompson, Ballmaier, Hellemann, Pham, & Kumar, 2008; Gunning-Dixon & Raz, 2003). In addition, other estimates of specific executive function measures, such as inhibition, have been linked to individual differences in frontal cortex volume (Adólfsdóttir et al., 2014). Interestingly, attempts with low-interference measures derived from the 2-back task found no volumetric association between target accuracy performance and the five prefrontal regions used in the current study (Nissim et al., 2017). Thus, using 2-back target accuracy as a measure of WM may obscure the link between executive function and frontal brain volume,

and the current results represents a first demonstration that IC is associated to relevant local brain volumes. It should be pointed out that a large portion of the variance could not be accounted for by our IC measures, indicating that executive functions are rather unspecific in nature (Friedman & Miyake, 2017; Stuss, 2011). Our findings are therefore in line with a recent study showing strong evidence for both domain-general and domain-specific neural functions working in a coexistent manner to resolve cognitive conflict (Hsu et al., 2017).

A range of tasks and cognitive processes have been associated with VLPFC functioning (Badre & Wagner, 2007; Alvarez & Emory, 2006), indicating that this region either is involved in multiple subprocesses or play a general cognitive role that is shared between many cognitive tasks. In the context of the present findings, VLPFC has been implicated in selection and resolution of interference from competing memory representations across a variety of WM tasks, such as *n*-back and recent probes tasks (Nelson, Reuter-Lorenz, Persson, Sylvester, & Jonides, 2009; Badre & Wagner, 2007; Nee et al., 2007; Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001). Although the precise role of this region remains unclear, our results adhere to the view that the VLPFC is relevant for keeping task-irrelevant information out of WM during maintenance and retrieval. Preventing competing representations from entering WM is one of the most fundamental aspects of successfully maintaining a desired representation, rendering IC a key factor for efficient WM functioning. It is also likely that an RT-based interference score, as used here, is capturing a component of executive control based on effort to resolve interference. Individuals with a larger brain volume in IC-relevant regions, such as the VLPFC, may have greater capacity to exert effort or recruit neural resources needed to overcome demanding and goal-irrelevant information. This nicely aligns with fMRI evidence showing that the VLPFC and other regions, such as insula, are more engaged in better-performing individuals in task paradigms that include inhibition (Cieslik et al., 2015; Jiang, Beck, Heller, & Egner, 2015; Dodds et al., 2011; Duncan & Owen, 2000). The insula, together with the VLPFC area, may therefore play a unique role in adapting to dynamic control demands such as conflict (Jiang et al., 2015).

Moreover, across participants, responses to familiar items were slower and less accurate compared with non-familiar items, which implicates the process of binding new item information to a specific context for familiar items (Mishra et al., 2013; Oberauer, 2005; Hedden & Park, 2003). This has been linked to prefrontal engagement during encoding (Becker, Kalpouzos, Persson, Laukka, & Brehmer, 2017; Murray & Ranganath, 2007; Addis & McAndrews, 2006). Specifically, caudal middle frontal GM volume has been positively associated with self-initiated encoding strategies (Husa et al., 2017), which could explain why our follow-up participants with marginally larger caudal middle frontal volume had a

small advantage in accurately resolving PI. Apart from deficient encoding of item–context associations, observed age effects in IC might also indicate that older adults are less efficient in unbinding no longer relevant item–context associations (Ecker, Oberauer, & Lewandowsky, 2014; Ecker, Lewandowsky, & Oberauer, 2013). Such an unbinding deficit can be characterized by goal-irrelevant retaining of information (Samrani et al., 2017; Shipstead et al., 2016; McCabe & Hartman, 2008), leading to a prolonged effect of PI. Many current models emphasize contextual binding as critical to successful WM function (Oberauer & Lin, 2017; Schneegans & Bays, 2017), and that such contextual binding may involve temporal information. Many studies have further implicated the VLPFC as an important region in contextual binding and source memory (Becker et al., 2017; Dulas & Duarte, 2012; Hales, Israel, Swann, & Brewer, 2009; see Mitchell & Johnson, 2009; Blumenfeld & Ranganath, 2007, for reviews), further suggesting that associative-like memory is important for IC, and these functions are also impaired with increasing age (Naveh-Benjamin, 2000; Chalfonte & Johnson, 1996). In addition, representation of temporal order information seems to largely engage the lateral pFC (Marshuetz, Smith, Jonides, DeGutis, & Chenevert, 2001). Given the observation of significant and co-occurring age-related decline in lateral pFC volume and deficits in associative binding, it is likely that age-related changes contribute to increased susceptibility for PI in WM.

This study failed to confirm expected relationships between change in IC and change in local brain volume. To date, only a handful of studies have demonstrated associations between change in cognition and change in brain volume in older adults (Gorbach et al., 2017; Persson et al., 2012; Murphy et al., 2010; Kramer et al., 2007; Mungas et al., 2005), and these have typically focused on episodic memory, rather than executive control functions. It may not be surprising, however, that we were unable to find a link between decline in IC and brain volume change 4–5 years after baseline. There are several reasons for this: First is the low test–retest reliability of our interference scores, and second, the relatively short time span between baseline and follow-up may impose restrictions to measurement of behavioral change. This is evident from the findings of nonsignificant change in interference between baseline and follow-up, even in the group of older individuals. Another point may be that what we observe is a lifelong association (Karama et al., 2014) between IC and GM volume and not necessarily attributed to the aging process, at least not for the short time span measured here. Many participants, regardless of age, exhibited improved IC over time, which makes it difficult to assess expected change–change links associated with the aging process. A similar pattern of improvement, also with verbal memory tasks, has been observed in previous longitudinal studies (Leong et al., 2017; Goh, An, & Resnick, 2012) and points to difficulties in estimating the true rate of cognitive decline in cognitive tasks where repeated testing masks genuine decline. Moreover, the time span for longitudinal analyses in the current study (4–5 years) may not have been enough to capture cognitive decline that might occur over longer time periods. A lack of change across shorter time intervals (<10 years) is a common finding in the literature, in particular in normal aging samples (e.g., Salthouse, 2009; Schaie, 2005).

Both AIS and RTIS were extracted from the same lure trials but were very differently related to brain volume, aging, and performance in other cognitive domains. The discrepancy between the two measures of IC used here showed RTIS to be related to brain volume and AIS to be more related to other accuracy-based cognitive measures, suggesting that these two estimates capture partly separate cognitive processes underlying interference resolution. Also, and importantly, participants with superior RTIS also had better AIS than the low-performing group, showing no indications of a typical speed–accuracy trade-off (e.g., Heitz, 2014). The group selection was therefore based on a true difference in the ability to control interference, with no indications of slower participants using time to be more accurate on interference trials. In addition, AIS and 2-back target accuracy, but not RTIS, were related to other accuracy-based measures of cognition. Note that accuracy and RT estimates, specifically those drawn from n-back, have been shown to be weakly associated with each other (Redick & Lindsey, 2013) and with other cognitive tasks (Jaeggi, Buschkuehl, Perrig, & Meier, 2010), suggesting that accuracy and RTs in the n-back task should not be interpreted interchangeably. Altogether, one possibility is that RTIS capture IC effort more precisely compared with decision-based measures such as accuracy—in this case, AIS and target accuracy.

The current study has a number of limitations that should be acknowledged. First, the n-back task used here included a rather limited number of trials for each condition, which may have implications for the robustness and reliability of the data. However, despite the limited number of trials, the interference effect was robust at the group level, showing that individuals were significantly slower and less accurate on familiar lure trials compared with nonfamiliar trials. Moreover, the relatively low number of participants that remained for follow-up testing may have resulted in low statistical power in detecting longitudinal effects. Somewhat unexpectedly, some relationships were only found in the follow-up data. Possibly, this may be explained by the dropouts being older and having worse performance compared with those that stayed in the study. The remaining participants at follow-up may, as a result, be a more salient representation of RTIS performance across age, seeing that a stable difference score is highly reliant on the amount of accurately answered lure trials. At the same time, an increased ratio of better performing individuals might have diffused the volumetric contrast in VLPFC between unaffected and affected individuals. Another limitation is that a single-sample study

design with only two measurement points was used. We were therefore not able to examine long-term trajectories of change, and this design also did not permit independent estimations of retest effects, which are known to influence longitudinal data (Salthouse, 2013, 2014; Ghisletta, Rabbitt, Lunn, & Lindenberger, 2012). Future work with three or more time points could reveal long-term trajectories of change that we are unable to show in the current study design and may also help in better estimating retest effects.

Here, we provide preliminary evidence for a link between GM volume and IC in WM. Individuals with superior ability to control interference had, on average, slightly larger brain volume in the VLPFC and insula, regions previously implicated in executive control functions. However, change in pFC volume was not related to change in IC. Cross-sectional analyses showed that older age was related to a reduced ability to control interference and also demonstrated that IC was related to performance across multiple cognitive domains. We believe that the present results constitute a step forward in emphasizing the use of a salient measure of IC, with the purpose of more precisely understanding how IC relates to brain correlates and performance across cognitive domains.

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